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EXAMINER
ANGELL, JON E

ART UNIT	PAPER NUMBER
1635	

MAIL DATE	DELIVERY MODE
07/25/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/604,945	BENTWICH, ITZHAK	
	Examiner	Art Unit	
	J. Eric Angell	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 May 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-23 and 33-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 August 2003* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/8/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Notice to Comply*.

DETAILED ACTION

This Action is in response to the communication filed on 5/8/2007.

The amendment filed 5/8/2007 is acknowledged and has been entered. .

Claims 21-23 and 33-35 are currently pending in the application and are addressed herein.

1. Applicant's arguments are addressed on a per section basis. The text of those sections of Title 35, U.S. Code not included in this Action can be found in a prior Office Action. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

Information Disclosure Statement

2. The information disclosure statement (IDS) submitted on 5/8/2007 is acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Sequence Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825. Specifically, Figures 12-14 of the Drawings contain nucleic acid sequences, but neither the Figures nor the Description of the Figures in the specification identify the sequences with an

appropriate sequence identifier (SEQ ID NO), as required. Accordingly the specification and the Drawings are objectionable.

Applicants are encouraged to review the entire disclosure for compliance with 37 C.F.R. §§ 1.821-1.825.

Applicant is requested to return a copy of the attached Notice to Comply with the response.

New Claim Rejection - 35 USC § 112, second paragraph

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 21-23, 33-35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

5. Claim 21 has been amended such that it encompasses an isolated nucleic acid consisting of 18 to 120 nucleotides wherein the sequence of the nucleic acid comprises ≥ 24 consecutive nucleotides of SEQ ID NO: 5264. However, SEQ ID NO: 5264 only comprises 24 nucleotides, as acknowledged by Applicants on page 3 of their response (see second to last paragraph). Since SEQ ID NO: 5264 only comprises 24 nucleotides, it is unclear how the claimed isolated nucleic acid could comprise more than 24 consecutive nucleotides of SEQ ID NO: 5264. Accordingly, claim 21 is indefinite. Furthermore, claims 22, 23, 31-33 are dependent claims which must encompass all embodiments of the claim from which it depends, in this case claim 21. Therefore, claims 22, 23, 31-33 are also indefinite.

New Claim Rejection - 35 USC § 112, first paragraph

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 21-23, 33-35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.**

37 CFR 1.118 (a) states that "No amendment shall introduce new matter into the disclosure of an application after the filing date of the application".

MPEP §2163.06 notes:

If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981).

MPEP §2163.02 teaches that:

Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application.

MPEP §2163.06 further notes:

When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or not "new matter" is involved. Applicant should therefore specifically point out the support for any amendments made to the disclosure.

First, as indicated above, claim 21 has been amended such that it encompasses an isolated nucleic acid consisting of 18 to 120 nucleotides wherein the sequence of the nucleic acid comprises ≥ 24 consecutive nucleotides of SEQ ID NO: 5264. However, SEQ ID NO: 5264 only comprises 24 nucleotides. Furthermore, the specification does not appear to disclose that the isolated nucleic acid can comprise more than 24 consecutive nucleotides of SEQ ID NO: 5264. On page 3 of the response, Applicants contend that support for this limitation can be found in Table 1. However, Table 1 only appears to disclose SEQ ID NO: 5264 as consisting of 24 nucleotides. Accordingly, claim 21 contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of an isolated nucleic acid sequence having ≥ 24 consecutive nucleotides of SEQ ID NO: 5264, a 24mer.

Next, claim 21 has been amended such that it encompasses an isolated nucleic acid consisting of 18 to 120 nucleotides wherein the sequence of the nucleic acid comprises a sequence at least 73.7% identical to nucleotides 51-59 of SEQ ID NO: 2194. Applicants assert that support for this limitation can be found in Table 2 which shows that nucleotides 51-68 of SEQ ID NO: 2194 can form a miRNA that binds to the target YWHAZ with 14 out of 19 bases complementary. Applicants contend that the ratio 14/19 expressed as a percentage rounded up to the nearest tenth is equivalent to 73.7% (see pages 4-5 of the response). However, simply because the specification has disclosed that SEQ ID NO: 2194 can form a miRNA that binds to the target YWHAZ with 14 out of 19 bases complementary does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of, or even contemplated isolated nucleic acid sequences which are at least 73.7%

identical to nucleotides 51-59 of SEQ ID NO: 2194. Accordingly, the disclosure does not provide the required support for the instantly claimed invention. Claims 22, 23, 33-35 are dependent claims that also encompass these limitations; therefore, claims 22, 23, 33-35 are rejected for the same reasons.

To the extent that the claimed compositions and/or methods are not described in the instant disclosure, claims 21-23, 33-35 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, since a disclosure cannot teach one to make or use something that has not been described.

Maintained Claim Rejection - 35 USC § 112, first paragraph

8. Claims 21-23, 33-35 also remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement (new matter) for the reasons below, which were set forth in the previous Office Action (12/8/2006).

No support has been found in the specification as originally filed for an isolated nucleic acid with size limitations of 18-120 nucleotides (e.g. as recited in claim 21). It is noted that the specification, including the indicated paragraphs, Tables and originally filed claims were reviewed and support for the indicated limitation could not be found.

In the response filed 5/8/2007, Applicants assert that support for the limitation 18-120 nucleotides can be found in paragraph 14, which Applicants quote as disclosing, " RNA encoded by the bioinformatically detectable novel viral gene is about 18 to about 24 nucleotides in length

and originates from an RNA precursor, which RNA precursor is about 50 to about 120 nucleotides in length." Applicants contend that based on this statement, nucleotides between 18 and 120 nucleotides in length are disclosed such that one of ordinary skill in the art would be able to conclude that the claimed subject matter is described in the specification.

However, the quoted statement does not provide support for nucleotides 18-120 nucleotides in length. It only provides support for nucleotides that are "about 18 to about 24 nucleotides in length" and nucleotides that are "about 50 to about 120 nucleotides in length." The statement cannot be considered for support for the full range of 18-120 because it does not disclose nucleotides which are 25-49 nucleotides in length. Therefore, Applicants arguments are not persuasive with respect to the rejection as indicated here.

It is noted that the other limitations which were indicated as being new matter in the 12/8/2006 Office Action as being new matter are no longer at issue in view of the amendment and/or Applicants arguments.

Maintained Claim Rejections - 35 USC §§ 101 and 112

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 21-23, 33-35 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or, alternatively, a well established utility, essentially for the reasons of record set forth in the 12/8/2006 Office Action.

In their broadest embodiments, the claims are drawn to isolated nucleic acid sequences which are 18-120 nucleotides in length and comprise nucleotides of SEQ ID No. 2194 or a complement thereof.

A review of the specification, which is over 28000 pages long, finds general assertions and statements that the present invention relates to a group of bioinformatically detectable novel genes, which Applicant refers to as "genomic address messenger" or "GAM" genes, which are believed to be related to the micro RNA (miRNA) group of genes.

The specification teaches that Micro RNAs (miRNAs), are short ~22nt non-coding regulatory RNA oligonucleotides, found in a wide range of species, believed to function as specific gene translation repressors, sometimes involved in cell-differentiation.

The specification makes general statements that the bioinformatically detectable sequences, GAMs, and the miRNAs they may encode may have utility for regulating target genes and possibly for treating disease.

However, the specification provides no direct or indirect evidence for any specific, substantial, or credible utility of the instantly claimed RNAs encoded by SEQ ID NO:2194 (or complement thereof). There is no disclosure indicating or suggesting that SEQ ID NO:2194 has itself ever been isolated or examined in any way, nor any evidence that the claimed RNA has, in fact, been isolated or prepared or studied or examined under any conditions. Any asserted utility for the claimed sequences appears to be merely speculation based on "bioinformatics," homology, and secondary structure predictions suggesting that the encoded RNAs are miRNAs because they have a miRNA-like hairpin structure and some degree of sequence homology to some unidentified target sequence. On this basis, and since other miRNAs are known to have

gene expression modulating properties, Applicant appears to be asserting that the bioinformatically detectable sequences, or GAMs, such as the RNAs encoded by SEQ ID NO:2194 also have utility.

However, that utility has not been clearly defined, nor does the prior art search of SEQ ID NO:2194 provide any substantial evidence to show that the RNAs of the size now claimed have any substantial, specific, or credible utility.

Applicant has not shown, and there is no evidence in the prior art to suggest, that the nucleic acids now claimed are expressed in any cell whatsoever. Indeed, the asserted utility and target gene of this and thousands of other miRNA-like sequences appears to be based purely on bioinformatic methods for predicting RNA folding and potential gene targets.

Krutzfeldt et al. (2006) *Nature Genetics* 38:514-519 state that, in general, the basis for these types of prediction programs is the degree of sequence complementarity between a miRNA and a target UTR, including the presence of a consecutive string of base pairs at the 5′ end of the miRNA known as a 'seed' or 'nucleus', and the cross-species conservation of this binding site. On average, 200 genes are predicted to be regulated by a single miRNA. The authors further state that reviewing the data provided by these algorithms determining candidate targets uncovers the entire gamut of gene categories, such as transcription factors, protein kinases, vesicular trafficking molecules and membrane receptors, suggesting that there is no apparent bias towards one particular function.

Accordingly, while the ability to predict hairpin-like structures and potential gene targets from genomic sequence information appears to be within the state of the art, Krutzfeldt et al. teach that validating the true biological function of any predicted miRNA sequence requires

analyzing miRNA expression patterns, as well as testing the effects of miRNA overexpression and underexpression under different conditions in living cells *in vitro* and *in vivo*.

Thus, while these methods, too, are within the level of skill in the art, Applicant has presented no evidence that any of these validation techniques have, in fact, been carried out with regard to the instantly claimed sequences. That is, no evidence can be found verifying or even suggesting that the sequences encompassed by the claims, including SEQ ID NO:2194, etc., actually gives rise to miRNAs in any cell or organism, and if it does, Applicant has not described or shown any specific, substantial, or credible utility for the expressed miRNA. The fact that an miRNA can regulate gene expression is not specific or substantial because 1) this activity is inherent to almost any miRNA, and 2) because Applicant has not taught any use or purpose for the inhibitory activity nor proposed any specific utility for the asserted down regulation of the target gene of the RNA now claimed.

For instance, Applicant has not provided evidence that the nucleic acid sequences encompassed by the claims play any role in disease. It appears that SEQ ID NO: 2194 may be part of the HIV genome, but there is no indication that SEQ ID NO: 2194 is actually processed in to a miRNA, and if it is, what function the miRNA would have when it is expressed. Accordingly, there is no evidence to suggest that the miRNAs nucleic acid sequences of the instant invention would provide any real world information for a specific use other than general knowledge as to understanding the biological function of the miRNA. Therefore, the information of record amounts to only a starting point and further experimentation would be required in order to identify the function of SEQ ID NO: 2194 and any miRNAs derived therefrom.

The specification generally asserts that a utility of the novel oligonucleotides of the present invention is detection of GAM oligonucleotides and of GR (Genomic Record) polynucleotides—that diagnosis of expression of oligonucleotides of the present invention may be useful for research purposes, in order to further understand the connection between the novel oligonucleotides of the present invention and disease and disease diagnosis and prevention purposes, and for monitoring disease progress.

However, none of these asserted uses meet the three-pronged requirement of 35 U.S.C. § 101 regarding utility, namely, that the asserted utility be credible, specific AND substantial.

This asserted utility is neither specific nor substantial. Since the same can be done with any polynucleotide, the asserted utility is not specific. Also, because the specification does not disclose any specific function for SEQ ID NO:2194, aside from indicating that it may encode an miRNA, it is unclear how or why one of skill in the art would use the information obtained by measuring SEQ ID NO:2194 or its DNA complements or expressed RNAs for any particular purpose aside from general research. Therefore, the asserted utility is not substantial since the application provides no teaching regarding how to use the sequences or expression data for any practical purpose beyond the art-recognized methods of gene expression analysis.

Accordingly, polynucleotide probes derived from the instant invention are simply research intermediates that may help scientists isolate the gene and conduct further experimentation. Such probes can only be used to detect or amplify the genetic material having the same structure as the probes themselves. The probes, vectors and gene expression inhibition systems would provide no immediate, real-world information about the overall structure or function of the underlying gene, for example, aside from its expression patterns.

Neither the instant specification nor the prior art presents any evidence that instant SEQ ID NO:2194, much less the claimed RNA equivalents or complements thereof have any specific biological function. No convincing evidence is found teaching any specific biological function for SEQ ID NO:2194 at all. In fact, no evidence is found suggesting or stating that the RNAs encoded by SEQ ID NO:2194 have been made, isolated, cloned, detected, expressed, or even analyzed in any living cell *in vitro* or *in vivo*.

In summary, no biological or biochemical function has been assigned to the claimed sequences, apart from the general assertions that it, like the thousands of other sequences described in the sequence listing, may correspond to a miRNA and have some direct or indirect relation to human biology and/or cell function.

Thus, the proposed utility of the sequences as therapeutic targets or agents, research tools, material resources for preparing diagnostic probes, vectors, and systems, are simply starting points for further research and investigation into potential practical uses of the claimed nucleic acid sequences.

Brenner v. Manson, 148 U.S.P.Q. 689 (U.S. 1966)

> The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility. Unless and until a process is refined and developed to this point—where specific benefit exists in currently available form—there is insufficient justification for permitting an applicant to engross what may prove to be a broad field.
>
> …a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.

Thus, the specification does not teach a specific and substantial utility for claimed sequences. No evidence has been presented showing or suggesting that any small RNAs derived

from SEQ ID NO:2194 is present in any cell, and, if so, what function these sequences perform. Accordingly, a credible, specific, and substantial nexus has not been established.

Claims 21-23, 33-35 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or, alternatively, a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Response to Arguments

Applicant's arguments filed 5/8/07 have been fully considered but they are not persuasive.

Applicant argues the specification identifies several particular target mRNA transcripts of interest for which the claimed polynucleotides may be used to regulate expression including the mRNA transcripts of the SLC4A4 and YWHAZ genes (see pages 9-10). Applicant asserts on the basis of Igarishi et al. J. Am. Soc. Nephrol (2001), that SLC4A4 is known to encode a kidney $Na^+ HCO_3^-$ transporter that is associated with type II renal tubular acidosis (proximal renal acidosis), and on the basis of Han et al. PNAS (1997) that YWHAZ encodes a protein that is implicated in nitrogenous and oncogenic transformation and which interacts with RIN1 which interacts with activated RAS and is implicated as being involved in tumorigenesis. Applicant contends that one of ordinary skill in the art would therefore recognize that the claimed polynucleotides may be used to regulate expression of a gene such as SLC4A4 or YWHAZ and thereby elucidate their roles in diseases. Applicant argues that whether or not the claimed

polynucleotides actually exist in a biological system, and whether the true biological function of any predicted miRNA sequence has been validated according to Krutzfeldt (cited by Examiner in the 12/8/2006 Office Action) are irrelevant. Applicants contend that the proper inquiry is instead whether a person of ordinary skill in the art would believe that the claimed polynucleotides may be used to modulate expression of the specific mRNA targets.

These arguments are not persuasive because the fact that the claimed nucleic acid may be used to regulate expression of a gene such as SLC4A4 or YWHAZ is speculative, based on bioinformatics comparisons only, with no evidence presented showing that the claimed nucleic acids, when expressed in vitro or in vivo would result in the inhibition of the asserted targets nor any credible representations that inhibition of the target would result in an effect of real world value, such as the treatment of any known disease or condition, nor any indication that inhibition if obtained would even result in a detectable phenotype of any practical use, for example, in the study of any disease. Further, the claims encompass not only the sequences encoding the purported miRNAs, but also variants and complements thereof, i.e., sequences antisense to said miRNAs. Applicant seeks to claim all such sequences and, as such, asserts that specific, substantial, and credible utilities exist for all these sequences.

Focusing on SEQ ID NO:5264, the argued utility that the claimed nucleic acid may be used to elucidate the role of SLC4A4 and YWHAZ is not specific because any nucleic acid that is or encodes an antisense sequence to a target may inhibit that target and therefore may be used to elucidate the biological nature of the target. Thus, the asserted utility is general, with no assurance that any useful information or result will be derived therefrom nor any guidance as to how to use the data obtained thereby to produce a useful result.

Furthermore, the targets themselves may be related to numerous conditions. The assertion that eliminating target expression will result in treatment effect is speculative. The Examiner is unable to find a single representative example in the specification or the prior art that the elimination of a target complementary to the claimed nucleic acids would produce the intended results. Moreover, eliminating the function of even a single gene can produce numerous effects, positive and/or negative. No evidence of any specific effect is neither presented, nor any proof-of-principle studies to show that the claimed sequence would in fact inhibit expression and produce the asserted effects.

Furthermore, the claimed nucleic acids would appear to encode candidate miRNA precursors. Thus further conjecture is necessary for one of skill to believe based on the specification that the precursors now claimed are processed into one or more mature miRNAs that actually downregulate the proposed target in a cell and that further the downregulation results in a predictable effect of real world value. No evidence is presented to suggest how or to what degree the preprocessed or mature miRNA is able to inhibit or regulate expression nor even whether the claimed nucleic acid would have any other effects confounding the intended effect.

Furthermore, Applicant is not claiming a single nucleic acid sequence but a large genus of DNA complements and equivalents thereof, including sequences at least 73.7% identical to the claimed nucleic acid sequence, as well as complements of any of these sequences. No evidence of any kind is present in the disclosure or the prior art linking any of these sequences to a utility of immediate, real world value.

The Application presents the basis for further research without any assurance that a utility of real world value will ever emerge. One of skill would not be led to believe the asserted

utilities are credible because as evidenced by Krutzfeldt et al. (2006) *Nature Genetics* 38:514-519, one of skill would ordinarily require additional in vitro and/or in vivo evidence before confirming the proposed biological activity and therapeutic utility.

It is noted that Igarishi et al., cited by applicant as evidence of SLC4A4 association with proximal renal tubular acidosis (pRTA), merely associates a nonsense mutation in a cotransporter gene (SLC4A4) with pRTA. The paper does not evidence SLC4A4 as therapeutic target, the inhibition of which arrests or inhibits cancer cell proliferation, for example. Also, Han et al. cited by applicant as evidence of YWHAZ implicated in nitrogenous and oncogenic transformation, merely indicates that YWHAZ (RIN1) interacts with RAS and cABL *in vitro* (see page 4958, second column under "RIN1-RAS Interaction"; and page 4959, first column under "RIN1-ABL Interaction"). Thus, there is no evidence that RIN1 interacts with RAS of ABL *in vivo,* which is the basis for the notion that YWHAZ is associated with transformation. Furthermore, the complexity of the diseases (pRTA and cancer), makes it difficult if not impossible to predict *a priori* whether the inhibition of any one gene will produce the desired treatment effect. Empirical evidence would be necessary, as taught by Krutzfeldt et al.

Thus, the utility proposed is general. Applicant has not established a nexus between the claimed nucleic acid and any specific or real world use.

Applicant has mined the genome using bioinformatics tools to identify candidate miRNA-like sequences with potential miRNA like functions including gene expression regulation. There is no disclosure of record to show how the alleged miRNA sequences function in vitro or in vivo if at all. No disclosure is presented to indicate the miRNAs are actually

expressed, or if expressed artificially by recombinant means would provide for any effect of immediate value to the skilled artisan such treatment effects. Furthermore, the claims are extremely broad, encompassing a multitude of different DNA sequences.

The skilled artisan would be led to believe only that the instantly claimed nucleic acids require further research to identify any real world use other than possible uses as research tools.

Thus, the specification does not teach a specific, substantial, or credible utility for SEQ ID NO:5264 or SEQ ID NO:2194, much less any of the complements or variants thereof encompassed by the claims. No target gene has been conclusively identified nor has any evidence been presented linking the claimed sequences with any target gene, biological function or disorder. Accordingly credible, specific, and substantial nexus has not been established and, thus, the specification also does not provide an enabling disclosure for the claimed invention.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Eric Angell whose telephone number is 571-272-0756. The examiner can normally be reached on Monday-Thursday 8:00 a.m.-6:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Douglas Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/J. E. Angell/
Primary Examiner
Art Unit 1635

Notice to Comply	Application No.	Applicant(s)	
	Examiner J. Eric Angell	Art Unit 1635	

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☐ 7. Other: _

Applicant Must Provide:

☒ An initial or **substitute** computer readable form (CRF) copy of the "Sequence Listing".

☒ An initial or **substitute** paper copy of the "Sequence Listing", as well as an amendment directing its entry into the **specification**.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216 or (703) 308-2923
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